REMARKS

Reconsideration of this application is requested.

The specification has been amended as required by the Examiner in ¶ 1, page 2 of the action. The applicants affirm their election of the Group I claims. The non-elected claims 5-14 have been canceled without prejudice to divisional filing.

Claim 1 has been amended to include the substance of claim 4 and claim 6. As a consequence, claim 4 has been canceled as redundant. Claims 2 and 3 have also been canceled in favor of the indicated amendment of claim 1.

New claim 15, which depends from claim 1, is drawn to the embodiment where the binding unit is derived from Camelids. See, for example, page 7, 1st and 2nd full ¶s and original claim 7 as support for claim 15.

The claims now in the case are amended claim 1 and new claim 15. These claims are thought to be in acceptable form, patentable over the prior art and otherwise allowable. Accordingly, allowance of the application is requested.

In support of allowance, the applicants comment as follows on the various numbered Sections of the action, beginning at page 3:

Section 4

The objection to the declaration is noted. However, the Examiner is requested to reconsider the objection. The declaration shows that the applicant Frenken signed his name and provided a date for the signature. This should be sufficient even though Frenken deleted matter under his signature. In any case, according to the applicants' file, the applicants' declaration as filed included a second replacement page which included Frenken's signature with no deletion. See last page of the attached copy of declaration as filed. In the circumstances, it is submitted that the declaration as submitted should be acceptable.

Section 5

The specification has been amended to include SEQ. ID NOS. in the brief description of the drawings and in amended claim 1. The changes should obviate the Examiner's objection to ¶s 5(a) and 5(b).

Section 6

The Examiner is requested to reconsider the Section 112, 1st ¶ rejection of claims 1-4 (now claim 1) in view of the indicated amendments to claim 1 wherein the linker is defined

as SEQ. ID NOS. 2, 3 or 4 and the binding unit has been defined as "a heavy chain variable domain derived from an immunoglobulin naturally devoid of light chains". While the applicants do not agree with the Examiner's position in rejecting claims 1-4 on written description grounds, the amendments to claim 1 should moot this issue as it is clear that the applicants' disclosure provides full and complete written description for the invention as defined by amended claim 1 (and new claim 15). Accordingly, reconsideration of the Section 112, 1st ¶ rejection is requested.

Section 7

It is also believed that the amendments of claim 1 should moot the Examiner's enablement rejection under Section 112, 1st ¶ as set forth in Section 7 of the action. The specification clearly provides sufficient guidance for one in the art to practice the invention as defined by amended claim 1. No undue experimentation is required as claim 1, as presented, is fully supported and exemplified by the disclosure. Claim 1 as amended defines the linking group in specific fashion. The same is true with respect to the binding unit. The recited "restricted conformational flexibility" is inherently satisfied by the specific amino acid sequences recited in claim 1. Those in the art are fully enabled to practice the invention as claimed on the basis of the applicants' detailed disclosure. Accordingly, reconsideration and withdrawal of the Section 112, 1st ¶ enablement rejection are requested.

Sections 8-9

The Examiner is also requested to reconsider and withdraw the Section 112 2nd ¶ rejection of the claims in view of the amendments to claim 1. The degree of restricted conformational flexibility is defined implicitly by the limitation of the claims to the sequences of the linkers identified by SEQ. ID NOS. 2, 3 and 4.

Section 10

The applicants do not agree with the Examiner's assessment of applicants' priority document. Nevertheless, claim 1 has been amended to specify a multivalent "antigen" binding protein.

Sections 11-12

The Examiner's position appears to be mooted in view of the amendment of claim 1 to call for the sequences of claim 4. As noted, this inherently defines the degree of restricted conformational flexibility.

Sections 13-15

The Examiner is requested to reconsider the Section 102(b) rejections of claims 1-4 insofar as this might be applied to claim 1 as amended. The references cited and applied in these sections of the action do not disclose the applications' method of claim 1 as now defined.

More specifically, the crux of the applicants' invention is that, as explained on page 6, lines 8 to 16 of the specification, the use of a polypeptide linking group, as defined, which confers restricted conformational flexibility in linking together the antigen binding units, provides multivalent antigen binding proteins that demonstrate increased affinity and increased sensitivity for diagnosis and detection. The Examiner's references teach the skilled person to select flexible linkers to connect binding domains. The applicants' invention, on the other hand, teaches the use of linkers which confer restricted conformation flexibility, i.e. the linkers disclosed in SEQ. ID NOS. 2, 3 and 4, in combination with heavy chain variable domains normally devoid of a light chain to achieve surprisingly advantageous properties compared to the use of "normal" flexible linkers.

Linkers falling within the scope of those identified by applicants' invention may have been used in the prior art for linking binding domains such as classical antibody fragments, comprising Vl and Vh domains that together form an antigen binding entity when juxtaposed in the required orientation, spacing and mutual interaction. However, said linkers have not been disclosed for linking heavy chains variable domains which are naturally devoid of a light chain to yield multivalent antigen binding molecules. More importantly, the prior art does not disclose or suggest that use of the applicants' linkers with limited conformational flexibility confers an increased binding affinity to the binding domains.

The VHHs of the current invention, which are structurally entirely different to Vl and Vh domains, comprise only a single variable domain that is capable of interacting to form an antigen binding molecule. The observation made by the present inventors that the indicated linkers which confer restricted conformational flexibility are capable of improving the affinity of VHHs and give better results in terms of affinity than flexible linkers, as demonstrated in this application, for instance in Example 1.5 on page 24 and in Figures 5, 6 and 7, is not disclosed or suggested by the Examiner's references as applied in Sections 13-15.

Accordingly, it is respectfully submitted that the Examiner's references do not anticipate the applicants' invention as claimed. Withdrawal of the Section 102(b) rejections as set out in Sections 13-15 of the action, with allowance of the applicants' claims, is therefore requested.

All of the Examiner's objections and rejections having been dealt with, the applicants submit that this application is in condition for allowance and such action is requested.

Respectfully submitted,

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